

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: June 10, 2014

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Subject: Review evaluates if a REMS is needed for Movantik

Drug Name(s): Movantik (naloxegol)

Therapeutic Class: peripherally-acting mu-opioid antagonist

Dosage form: oral tablet

Application Type/Number: NDA 204-760

Applicant/sponsor: AstraZeneca Pharmaceuticals LP

OSE RCM #: 2013-2137

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1 INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the NDA 204-760 for Movantik (naloxegol) to assess the need for a Risk Evaluation and Mitigation Strategy (REMS). A 505(b)(1) application for Movantik was received by the Division of Gastroenterology and Inborn Errors Products (DGIEP) from AstraZeneca Pharmaceuticals on September 16, 2013 to treat opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. The Sponsor did not propose a REMS for Movantik.

1.1 PRODUCT BACKGROUND

Movantik is a peripherally-acting mu-opioid receptor antagonist (PAMORA) and pegylated¹ derivative of the mu-opioid antagonist naloxone that primarily exerts its pharmacologic activity in the gastrointestinal tract, to decrease opioid-induced constipation without affecting opioid-mediated analgesia in the central nervous system (CNS). As a pure (full) antagonist at mu-opioid receptors (highest binding affinity), antagonist at delta-opioid receptors and weak partial agonist at kappa-opioid receptors, Movantik's pharmacologic profile is unique in the class of PAMORAs.

The proposed indication is for the treatment of OIC in adult patients with chronic non-cancer pain. Dosing for Movantik is as follows:

- Take one 25 mg tablet daily; to be taken in the morning on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours post-meal.
- Discontinue all current maintenance laxative therapy (b) (4)
- Reduce Movantik dose to 12.5 mg once daily in patients unable to tolerate the 25 mg once daily dose.

Patients are instructed to discontinue Movantik and contact their physician if opioid pain medication is discontinued (b) (4)

Movantik should not be used by patients with known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction. In addition, patients with conditions associated with blood-brain-barrier disruptions (b) (4) risk for opioid withdrawal or reversal of analgesia with the use of Movantik.

1.2 DISEASE BACKGROUND

Pain management is often described as one of the greatest challenges of clinical medicine, and opioid analgesics have become a mainstay for the treatment of chronic pain. According to a 2011 report from the Executive Office of the President of the United States, the number of opioid prescriptions dispensed by retail pharmacies increased 48%

¹ Pegylation is the process of polyethylene glycol (PEG) attachment to another molecule (often a drug). Pegylation reduces Movantik's permeability which decreases CNS penetration.

between 2000 and 2011; 174 million opioid prescriptions were dispensed in 2000, rising to 257 million by 2011.² While opioids are highly effective at pain management, they are associated with potentially use-limiting side effects.

Constipation is the most frequently reported side effect with chronic opioid use. Plausible etiologies for OIC include impaired defecation response, reduced peristalsis of the small intestine and colon, increased water and electrolyte absorption, and increased anal sphincter tone. Mu and delta opioid receptors located on smooth muscle in the gut are believed to have a significant role in gastrointestinal motility. Pure opioid antagonist and drugs with opioid agonist-antagonists properties may lower the frequency of OIC as compared to pure agonists.³

The constipating effects of opioid use are dose-related and tolerance to this symptom does not tend to occur. Prophylaxis with increased fiber and fluid intake is often considered with the initiation of opioid therapy however, this approach is insufficient to fully address the needs of many patients. While laxatives such as bulk-forming (e.g., methylcellulose), osmotic (e.g., polyethylene glycol), saline (e.g., magnesium hydroxide), stool softeners (e.g., docusate sodium) and stimulant (e.g., bisacodyl), are also commonly used to address OIC, these strategies are often an ineffective long-term strategy, particularly in patients requiring chronic opioid therapy.

Approved treatments for opioid-induced constipation include the following:

- lubiprostone
- methylnaltrexone

None of the currently available products specifically indicated to treat OIC are approved with a REMS. The PAMORA alvimopan has been used off-label for treating OIC⁴, although the extent of this off-label use is unknown. Alvimopan is approved with a REMS to mitigate the potential risk of myocardial infarction.

1.3 REGULATORY HISTORY

April 23, 2013: Pre-NDA (Type C) Meeting in which the Agency requested additional post-hoc analyses of data regarding opioid withdrawal and cardiovascular effects with Movantik use.

September 16, 2013: AstraZeneca submitted a 505(b)(2) NDA for Movantik.

March 31, 2014 (Mid-cycle Communication): Applicant informed that the Agency does not anticipate that the application will require a REMS.

² Executive Office of the President of the United States. Epidemic: Responding to America's Prescription Drug Abuse Crisis (2011). Available at: http://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan.pdf.

³ Herndon, C., Jackson, K., Hallin, P. (2002). Management of Opioid-Induced Gastrointestinal Effects in Patients Receiving Palliative Care. *Pharmacotherapy*, 1-15.

⁴ Sharkey K.A., Wallace J.L. (2011). Chapter 46. Treatment of Disorders of Bowel Motility and Water Flux; Anti-Emetics; Agents Used in Biliary and Pancreatic Disease. In Brunton L.L., Chabner B.A., Knollmann B.C. (Eds), *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e*. Retrieved June 09, 2014 from <http://accessmedicine.mhmedical.com/content.aspx?bookid=374&Sectionid=41266256>.

2 MATERIALS REVIEWED

The following are a list of materials used to inform the review:

- Johnson PA. Clinical Review for NDA 204-760, dated May 9, 2014
- AstraZeneca Pharmaceuticals. Draft label for Movantik (naloxegol), dated May 12, 2014
- DGIEP Mid-Cycle Communication to AstraZeneca, dated March 31, 2014
- Dunmon P. Division of Cardiovascular and Renal Products (DCaRP) Response to Consultation Request for Movantik (naloxegol), dated March 10, 2014
- Johnson PA. Mid-Cycle Meeting Slides-Clinical for Movantik (naloxegol), dated February 27, 2014
- Kilgore E. Division of Anesthesia, Analgesia and Addiction Products (DAAAP) Response to Consultation Request for Movantik (naloxegol), dated January 30, 2014
- AstraZeneca Pharmaceuticals. Clinical Overview for Movantik (naloxegol), received August 6, 2013

3 REVIEW FINDINGS FOR MOVANTIK

3.1 OVERVIEW OF CLINICAL PROGRAM FOR MOVANTIK

Movantik's safety and effectiveness in the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain was established based on the following clinical studies:

Pivotal Studies

Study 04 and Study 05: Phase 3, randomized, double-blind, placebo-controlled, multi-center, parallel group studies

Both studies were designed to compare the efficacy of two doses of naloxegol (12.5 mg and 25 mg) with placebo for the treatment of patients with non-cancer pain and OIC.⁵ Patients (N=652/Study 04; N=700/Study 05) were randomized 1:1:1 to receive Movantik oral tablet (12.5 mg or 25 mg) or placebo tablet once daily a 12-week treatment period.

Supportive Studies

Study 07: Phase 3, randomized, double-blind, placebo-controlled, safety extension study

The study was designed to evaluate the long-term safety and tolerability of Movantik. A total of 302 patients⁶ completing Study 04 were enrolled to receive Movantik oral tablet (12.5 mg or 25 mg) or placebo tablet once daily for an additional 12 weeks.

⁵ The study was designed to enroll patients with confirmed OIC who were on stable maintenance opioid therapy consisting of 30 mg – 1000 mg per day oral morphine or equianalgesic amounts of 1 or more opioid therapies, for at least 4 weeks prior to screening. Study patients also had a history of fewer than 3 spontaneous bowel movements per week and at least one symptom of OIC.

⁶ A total of 297 patients received the study treatment.

Study 08: Phase 3, randomized, open-label, parallel group, long-term safety study

- The study was designed to evaluate the long-term safety of Movantik. A total of 844 patients⁷ were randomized in a 2:1 ratio to receive Movantik 25 mg oral tablet once daily or Usual Care (as determined by the physician)⁸.

3.1.1 Efficacy

The primary efficacy endpoint was response (responder rate) to Movantik during weeks 1 through 12. A “responder” to Movantik was defined as a patient with 1) at least 3 spontaneous bowel movements (SBMs)⁹ per week, and 2) at least a 1 SBM per week increase (over baseline) for at least 9 of the 12 treatment weeks, and 3 of the last 4 treatment weeks during the double-blind treatment period.

Statistical significance was achieved for both Movantik doses compared to placebo in Study 04; response rates were 40.8% (p=0.015) and 44.4% (p=0.001) for the 12.5 mg and 25 mg doses respectively. While statistical significance was also achieved for Movantik 25 mg in Study 05 with a response rate of 39.7% (p=0.021), the difference in response rate between Movantik 12.5 mg and placebo was not statistically significant (p=0.202).

***DGIEP Clinical Reviewer Comment:** The 25 mg efficacy data was reproduced in both Phase 3 confirmatory studies—04 and 05. However, the 12.5 mg naloxegol dose was only shown to have efficacy statistically significantly different from placebo in Study 05. Therefore, given the lack of serious safety concerns with the 25 mg dose, I recommend approval of only the 25 mg dose for adult patients with OIC.¹⁰*

Note: *The 12.5 mg dose will be available on the market for special populations.*

3.1.2 Safety

The Movantik safety population was defined as all randomized patients receiving at least one dose of study drug. Within this broader safety population, the clinical review of safety focused on the following three primary analysis sets:

- 12-week safety pool (Studies 04 and 05)
- Placebo-controlled safety pool (Studies 04, 05, and 07)
- 52-week safety pool (Study 08)

In the 12-week safety pool, adverse events (AEs) were reported in 52.4% and 63.5% of patients in the Movantik 12.5 mg and 25 mg groups respectively. The increase in AEs

⁷ 760 new patients and 84 roll-over patients from Study 05 or Study 07.

⁸ There was no specific rescue laxative protocol for patients in the Usual Care group however these patients were prohibited from using methylnaltrexone or naloxone-containing products.

⁹ A spontaneous bowel movement (SBM) was defined as a BM without the use of rescue laxatives (bisacodyl or enema) administered in the previous 24 hours.

¹⁰ Johnson PA. Clinical Review for NDA 204-760, dated May 9, 2014.

between the two dosage strengths was primarily due to GI-related events. Abdominal pain was the most common AE reported in both Movantik dose groups. The incidence of AEs was higher with Movantik 25 mg than in patients receiving *Usual Care* (8.2% difference) in the 52-week safety pool.

A total of 7 deaths were reported during the Movantik clinical development program; there was no conclusive evidence to suggest that these deaths were related to Movantik use.

The incidence of serious adverse events (SAEs) was the same for Movantik 12.5 mg and placebo (4.5% in both groups); there was a slightly lower incidence with Movantik 25 mg (4.1%), based on data from the 12-week safety pool. The incidence of SAEs was higher in patients receiving *Usual Care* (11.1%) vs. Movantik 25 mg (8.6%) in the 52-week safety pool.

DGIEP Clinical Reviewer Comment: *There was a trend seen of increasing AEs in all Phase 3 studies for patients in the naloxegol [Movantik] 25 mg group (driven mainly by GI AEs). The opposite trend was seen in the subset of SAEs which confirms that the while there were more AEs in the higher naloxegol [Movantik] dose group this was not driven by SAEs.*¹¹

3.2 SAFETY CONCERNS

The class of peripherally acting mu opioid receptor antagonists (PAMORAs) has been associated with adverse events including cardiovascular events, bowel perforation, and opioid withdrawal.

3.2.1 Cardiovascular Events

Major Adverse Cardiovascular Events (MACE) were pre-specified as AEs of special interest based on a potential cardiovascular signal (myocardial ischemia) observed in a long-term safety study with the PAMORA alvimopan, and based on findings from a Phase 1 dog telemetry study to suggest a potential decreased BP and heart contractility with Movantik.

The total number of MACE with Movantik was low, with an incidence rate of 0.5 % for both Movantik 15 mg (0.2 % with Movantik 25 mg) and placebo in the 12-week safety pool. The incidence of MACE events in the 52-week safety pool was 0.4% with Movantik 25 mg compared to 0.7% with *Usual Care*.

Cardiovascular safety for Movantik was evaluated by the Division of Cardiology and Renal Products (DCaRP), and the DCaRP reviewer concluded the following:

DCaRP Reviewer Comment: *There is no definitive CV safety signal from naloxegol's [Movantik's] preclinical data, ECG data and TQT study, clinical vital sign data (changes in SBP, DBP, and HR), or MACE outcomes (stroke, MI, CV death, hospitalization for unstable angina, hospitalization for CHF).*¹²

¹¹ Johnson PA. Clinical Review for NDA 204-760, dated May 9, 2014.

¹² Dunnmon P. Division of Cardiovascular and Renal Products (DCaRP) Response to Consultation Request for Movantik (naloxegol), dated March 10, 2014.

The clinical reviewer (A. Peterson Johnson) provided the following additional comment:

DGIEP Clinical Reviewer Comment: *While there does not appear to be a CV safety signal in the naloxegol [Movantik] program, it will be important to hear the opinion of the experts at the AC [Advisory Committee meeting] regarding the entire PAMORA class. Once the entire class has been discussed at the AC, a decision regarding the naloxegol [Movantik] program and the need for a pre-market CV safety study will be made by the review team.*¹³

3.2.2 Bowel Perforation

Serious and in some cases fatal events related to bowel perforation have been reported with the use of the PAMORA methylnaltrexone. Cases of bowel perforation with methylnaltrexone were primarily observed in patients with advanced illness and underlying conditions that reduced the structural integrity in the wall of their GI tract (e.g., cancer, peptic ulcer, Ogilvie's syndrome).

While no cases of bowel perforation were reported or adjudicated in the Movantik clinical development program, the risk of bowel perforation will be included in the CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections of the Movantik label due to the risk of bowel perforation associated with other drugs in the class.

3.2.3 Opioid Withdrawal

Symptoms of opioid withdrawal have been reported with the use of the PAMORA methylnaltrexone. Naloxegol has limited capacity to pass through the blood brain barrier (BBB) with central opioid antagonism unlikely to occur at doses up to 10X the therapeutic dose. Patients with conditions that disrupt the BBB may be at an increased risk for opioid withdrawal due to a potential for increased uptake of Naloxegol into the CNS. Further, there are concerns that withdrawal could affect the autonomic nervous system causing hemodynamic changes that could increase a patient's risk for cardiovascular-related adverse events.

To further quantify the potential risk for opioid withdrawal with Movantik, data was collected in Phase 3 studies on 1) opioid dose, 2) opioid withdrawal signs/symptoms (primarily assessed by the modified Himmelsbach Scale¹⁴), and 3) changes in pain intensity (as measured by daily entries in an electronic diary).

The overall incidence of opioid withdrawal symptoms in the 12-week safety pool was 2% with Movantik and <1% with placebo. A total of 13 patients (one patient received placebo and twelve patients were Movantik-treated) in the Movantik clinical development program were coded by study investigators as having "drug withdrawal syndrome (DWS)." The 12 patients receiving Movantik were being treated with the

¹³ Johnson PA. Clinical Review for NDA 204-760, dated May 9, 2014.

¹⁴ The modified Himmelsbach Scale (mHS) is a clinician observer-rated scale in which patients are rated with respect to specific opioid withdrawal-related symptoms observed at the time of assessment.

following opioids for their pain conditions: Methadone (n=4), Morphine (n=4), Oxycodone (n=2), Hydrocodone (n=1), and Percocet (n=1).

Study investigators concluded that there appeared to be no confounding factors to explain the withdrawal events observed in the methadone treated-patients or in one of the patients receiving oxycodone.¹⁵ The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) was consulted by DGIEP to further evaluate the risk for opioid withdrawal with Movantik. The DAAAP reviewer concluded that while there was evidence of opioid withdrawal with Movantik compared to placebo, “the overall incidence was generally low.”¹⁶

The DAAAP reviewer provided the following insight into the potential for opioid withdrawal with Movantik, a drug whose primary pharmacologic activity is at mu opioid receptors in the GI tract:

***DAAAP Reviewer Comment:** There are mu opioid receptors located in the periphery, and not just the GI tract. The intended mechanism of action of naloxegol [Movantik] is local opioid reversal in the GI, and based on the GI symptoms, this is consistent with the GI symptoms experienced with centrally-mediated opioid reversal. It is unclear whether possible opioid withdrawal symptoms such as diaphoresis, chills, rhinorrhea, and yawning are secondary to the local effects from the GI pain, reflect activity at other peripheral mu receptors, or possible some central effects.*¹⁷

DGIEP proposed labeling under **WARNINGS AND PRECAUTIONS** is as follows:

5. (b) (4) Opioid Withdrawal

Symptoms consistent with opioid withdrawal occurred in some patients in clinical trials [see *Adverse Reactions (6.1)*]. Symptoms included but were not limited to hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning. In addition, patients receiving methadone as therapy for their pain condition were observed in clinical trials to have a higher frequency of gastrointestinal adverse events (such as abdominal pain and diarrhea) than patients not receiving methadone.

4 DISCUSSION

Patients with chronic pain on opioid analgesics often experience painful bouts of constipation that can significantly impact quality of life and place limitations on the use of opioids in pain management. In this population of patients, when lifestyle changes, laxatives and other approaches become insufficient to address the constipating effects of opioids, the use of opioid antagonists may present a viable option.

¹⁵ One of the morphine patients was labeled as “insufficient information.”

¹⁶ Division of Anesthesia, Analgesia and Addiction Products (DAAAP)- Response to Consultation Request for naloxegol/NDA 204-760 (E. Kilgore), dated January 30, 2014.

¹⁷ Kilgore E. Division of Anesthesia, Analgesia and Addiction Products (DAAAP) Response to Consultation Request for Movantik (naloxegol), dated January 30, 2014.

Movantik is a peripherally acting mu-opioid antagonist and derivative of naloxone that acts in the gastrointestinal tract to decrease the constipating effects of opioids without impacting opioid-mediated analgesia in the CNS.

The benefits of Movantik 25 mg were demonstrated in both pivotal studies, and include the following:

- Statistically significant increase in spontaneous bowel movement (SBM) without the use of rescue laxatives.

The most common AE observed in Phase 3 studies was abdominal pain, and overall, the incidence of AEs typically associated with the PAMORA class of drugs (opioid withdrawal and cardiovascular-related events) was low with Movantik. While Movantik is a derivative of naloxone, the drug exerts its primary mechanism of action in the periphery therefore, the high incidence of severe and abrupt opioid withdrawal and other CNS-mediated AEs reported with naloxone, was not observed with Movantik.

Reports of bowel perforation have been documented with the use of the PAMORA methylnaltrexone, however, no cases were observed in the Movantik trials. To address the potential risk for bowel perforation, risk information will be included in the Contraindications, and Warnings and Precautions sections of the prescribing information (PI). Risk information will also be included in the Warnings and Precautions section of the PI regarding the risk for opioid withdrawal (see section 3.2.3 above for DGIEP proposed labeling).

While there does not appear to be a cardiovascular safety signal with Movantik, the need for a pre-market cardiovascular safety study for Movantik will be determined based on discussion of cardiovascular risks associated with the PAMORA class of drugs, at an Anesthetic and Analgesic Drug Products Advisory Committee Meeting scheduled for June 11-12, 2014.

Based on the currently available data, DRISK believes that labeling will be sufficient to address the aforementioned risks; therefore, additional risk mitigation strategies are not warranted.

5 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for Movantik at this time. Movantik has proven efficacy in the treatment of OIC in adult patients with chronic non-cancer pain. While there are serious risks of concern with the PAMORA class of drugs, there was no signal of an increased risk of these events with Movantik in the premarketing safety database. Thus, the benefit-risk profile for Movantik is acceptable and the risks can be mitigated through professional labeling.

Should DGIEP have any concerns or questions, or feel that a REMS may be warranted for this product, please send a consult to DRISK.

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/s/

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